Emergency extracranial-intracranial bypass to revascularize salvageable brain tissue in acute ischemic stroke patients

Burkhardt, Jan-Karl ; Winklhofer, Sebastian ; Fierstra, Jorn ; Wegener, Susanne ; Esposito, Giuseppe ; Luft, Andreas ; Bozinov, Oliver ; Regli, Luca

DOI: https://doi.org/10.1016/j.wneu.2017.10.005

Originally published at:
Burkhardt, Jan-Karl; Winklhofer, Sebastian; Fierstra, Jorn; Wegener, Susanne; Esposito, Giuseppe; Luft, Andreas; Bozinov, Oliver; Regli, Luca (2018). Emergency extracranial-intracranial bypass to revascularize salvageable brain tissue in acute ischemic stroke patients. World Neurosurgery, 109:e476-e485.
DOI: https://doi.org/10.1016/j.wneu.2017.10.005

Manuscript type: original article

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Authors: Jan-Karl Burkhardt, MD[1] , Sebastian, F.-X. Winklhofer, MD[3] , Jorn Fierstra, MD PhD[1] , Susanne Wegener, MD[2] , Giuseppe Esposito, MD, PhD[1] , Andreas Luft, MD[2] , Oliver Bozinov, MD[1] and Luca Regli, MD[1*]

Affiliations: 1 Department of Neurosurgery, 2 Department of Neurology, 3 Department of Neuroradiology, University Hospital Zurich, University of Zurich, Zurich, Switzerland

***Corresponding Author:**

Luca Regli, MD

Department of Neurosurgery, University Hospital Zurich, University of Zurich, Frauenklinikstr.10, 8091 Zurich, Switzerland

Tel.: +41/ 44 255 1111, Fax.: +41/ 44 255 1111, E-Mail: luca.regli@usz.ch

Formatiert: Deutsch (Schweiz)

Formatiert: Deutsch (Schweiz)

Keywords: Emergency bypass; cerebral revascularization; acute stroke; perfusion/diffusion mismatch

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Abstract

Objective: To present an algorithm based on clinical and radiological factors including MR perfusion/diffusion mismatch (MR-PDM) for the indication of urgent cerebral bypass in patients with acute ischemic stroke

Methods: Analysis of clinical and radiological data on eight consecutive patients undergoing urgent cerebral revascularization for acute ischemic stroke due to occlusion of the internal carotid or middle cerebral artery between 2012 and 2015. All patients were either not eligible or failed emergent endovascular revascularization. Indication for urgent bypass was based on both clinical worsening and MR-PDM, indicating a threat for stroke extension. Clinical outcome was measured using NIHSS and mRS before and after bypass surgery, at 3 months and at last follow-up (LFU).

Results: All patients presented clinical worsening after initiation of acute stroke treatment. Cerebral revascularization was performed 9.6 hours (SD 9.0, range 3-30 hours) after clinical worsening. All patients had a preoperative MR-PDM. There were no bypass complications such as anastomosis failure or postoperative hemorrhage. MR diffusion ratio before and after bypass was stable or improved in 7 patients and progressed in 1 patient without clinical worsening. MR-PDM and perfusion improved in all 4 patients studied with postoperative MRI. Clinical outcome was favorable with a median improvement of 7 points of the NIHSS and of 2 points of the mRS at LFU.

Conclusions: In a highly selected group of patients presenting with acute ischemic stroke based on an algorithm indicating salvageable brain tissue cerebral revascularization can be safely performed in an emergency setting with favorable clinical outcome.

Introduction

The rationale for emergent intravenous thrombolysis or intraarterial thrombectomy in patients with acute ischemic stroke is to achieve immediate reperfusion of brain tissue at risk of dying and improve clinical outcome.[1-3] Recent randomized clinical trials showed that patients with acute ischemic stroke treated with endovascular intraarterial thrombectomy in addition to intravenous thrombolysis (ivt) benefit more than patients treated with ivt alone (MR CLEAN, SWIFT, SWIFT PRIME, ESCAPE, EXTEND-IA, TREVO-2 trials).[4-10] These results in acute ischemic stroke contrast with chronic steno-occlusive ischemic disease, in which randomized trails failed to show that surgical revascularization is superior to best medical treatment, mainly because of the peri-operative morbidity (COSS trial).[11-13]

The success of urgent endovascular revascularization in patients with acute stroke support the concept of penumbra around an ischemic core, defined as hypoperfused brain tissue, which can be salvaged, if blood flow is restored quickly enough.[14] To evaluate if a revascularization intervention makes sense the clinicians need to determine if brain tissue is still “alive” and if brain tissue is “at risk”. “Perfusion/diffusion mismatch” on magnetic resonance (MR) imaging and “perfusion/volume” mismatch on computed tomography perfusion (CTP) are two imaging modalities used in clinical practice as surrogate marker of penumbra.[15-17]

Based on the above results we hypothesized that in a highly selected group of patients with persistent penumbra after acute ischemic stroke and who were not eligible or failed endovascular revascularization, urgent surgical revascularization may be beneficial. The

aim of this study was to analyze the feasibility of urgent surgical revascularization in acute ischemic stroke and to report patient outcome and imaging perfusion changes.

Methods

Patient data and bypass indication

This study was approved by the institutional review board from the University of Zurich Switzerland (KEK-StV-Nr. 11/14). From our prospective database, we extracted all patients who underwent surgical cerebral bypass revascularization and identified those in whom the indication was "acute ischemic stroke" between August 2012 and August 2015 at the Department of Neurosurgery, University Hospital Zurich, Switzerland.

Patients and relatives were informed that management recommendation was based on patient specific characteristics and an interdisciplinary consensus decision of the cerebrovascular team composed at least of a senior cerebrovascular neurologist, neurointerventionalist and neurosurgeon. They were also informed that there is currently no evidence to support a benefit of such a revascularization procedure.

Urgent surgical revascularization was defined as a procedure performed as soon as possible, but no later than 48 hours after the decision to revascularize was taken by the cerebrovascular team. All of the following criteria had to be fulfilled to justify an urgent bypass: 1) patients with acute stroke and minor (NIHSS 1-4) to moderate stroke severity (NIHSS 5-15) at admission; 2) endovascular revascularization was not feasible or had failed as treatment option; 3) clinical worsening or symptom fluctuation (NIHSS <15) <72h after symptom onset, despite best medical treatment; 4) MR diffusion to perfusion mismatch or CT volume to perfusion mismatch (>120%), despite best medical treatment;

5) no large stroke (<10cm^2, edema or hemorrhage on the last imaging) and 6) patient was independent before admission (mRS<2).

Eight patients where identified using these criteria. Medical and operative reports and neuroimaging studies were reviewed. Pre- and postoperative clinical condition (mRS, NIHSS) and surgical complications including bypass patency and ischemia were assessed from our prospective database.

Clinical assessment

Initial management at the emergency room and stroke unit was according to clinical standards and included Doppler flowmetry, maintenance of a high-normal blood pressure (BP) and mean arterial pressure (MAP) range as well as intravenous thrombolysis, and antiplatelet medication. Patients in this series were not candidate for (n=5) or failed (n=3) emergent endovascular revascularization. Clinical status and symptoms at admission, discharge, 3 month follow-up and last follow-up were recorded using the National Institutes of Health Stroke Scale (NIHSS) and modified Ranking Scale (mRS).

Radiological assessment

Head/neck CT including CT angiography (CTA) and CTP and MRI including MR angiography (MRA), MR diffusion (MR-DWI) and MR perfusion (MR-PWI) were performed to detect ischemia, perfusion/diffusion mismatch, and main trunk stenosis or occlusion. In addition, 3 patients underwent a digital subtraction angiography (DSA) in the acute phase for emergent endovascular revascularization: in 2 patients it turned out to be non-feasible to remove the clot with the clot retriever and in 1 patient clot removal

was successful, but vessel re-occluded and stenting failed. In all other 5 patients endovascular revascularization was not considered to be feasible by the neuroradiologists.

The following MR-PWIand MR-DWI measurements were analyzed using a dedicated workstation (syngo MultiModality Workplace, Version syngo.via Client 3.0; syngo.MR Neuro Perfusion application, syngo.via VA 30; Siemens Healthcare, Erlangen, Germany): mean transit time (MTT), time to peak (TTP), cerebral blood flow (CBF), and cerebral blood volume (CBV). In addition, DWI/TTP mismatch before and after bypass was analyzed using manually drawn region of interest (ROI) measurements to acquire the area (cm2) of the largest extension of DWI and PWI changes in axial slices. In a similar fashion the area of diffusion restrictions were analyzed in DWI before and after bypass surgery and the ratio among those two values was calculated in percent. Patients presenting with DWI/TTP mismatch Type I (PWI >DWI), the main and most common pattern of perfusion-diffusion mismatch types by showing larger lesions on PWI than DWI, were defined as candidates for revascularization therapy.[18] MTT, TTP, CBF, CBV ratios indicate normalized values of the ipsilateral hemisphere (stroke) in relation to the contralateral non-affected hemisphere. DWI/TTP mismatch is within the ipsilateral hemisphere only. For 1 patient CTP was measured using Syngo MultiModality Workplace (syngo CT Neuro Perfusion, Version syngo. via Client 3.0, Siemens Healthcare, Erlangen, Germany).

Surgical bypass strategies

Urgent bypass was performed with the goal to augment blood flow to the territory presenting the mismatch. Intraoperative indocyanine green (ICG) videoangiography was used to select the recipient cortical artery. An M4 segment of the middle cerebral artery (MCA) showing delayed or retrograde filling on ICG was selected.[19] After bypass, intraoperative ICG videoangiography and Doppler flowmetry were used to determine bypass patency and measure blood flow.

Perioperative medical management during emergency bypass revascularization

Antiplatelet treatment using aspirin 100mg per day was started as soon as possible after the acute stroke event and maintained during as well as after surgery. An intraoperative thrombocyte-aggregation test (Multiplate®, Verum Diagnostica GmbH, Munich, Germany) was performed to exclude aspirin resistance before the micro-anastomosis. Meticulous blood pressure control was pursued, with strict avoidance of hypotensive episodes during the whole perioperative period, aiming at high-normal range of BP (>140mmHg systolic RR) and MAP (>110mmHg).

Statistical Analyses

Continuous variables were expressed as means plus or minus standard deviations (SD) and range. Categorical variables were expressed as frequencies with percentages. PWI ratios of MTT, CBF, CBV and TTP as well as DWI/TTP mismatch were presented using box plots. Due to the small sample size neither univariate nor multivariate testing was performed.

Results

General patient data and bypass strategy

In terms of preexisting cardiovascular risk factors, 6 patients were hypertensive and on antihypertensive medication, 1 patient was on aspirin 100mg/d, and another patient on clopidogrel 75mg/d both for coronary stenting. The patient on aspirin was continued on aspirin 100mg/d and the patient on clopidogrel was switched to aspirin 100mg/d on admission. All other 6 patients received aspirin 300mg loading dose at admission, followed by 100mg/d perioperatively. None of these patients showed an aspirin resistance and therefore dose escalation was not needed.[20] Three patients were smokers and one of the patients had type 2 diabetes. (Table 1)

Urgent bypass revascularization was successful in all consecutive 8 patients (4 females; mean age 65 years, SD 12.8, range 45-81) using an end-to-side extracranial-intracranial (EC-IC) bypass. Seven patients had a superficial temporal artery (STA) - MCA and 1 patient had a posterior auricular artery (PAA) - MCA bypass (figure 1). Mean time between indication for bypass and surgery was 9.6h (SD 9.0, range 3-30) after clinical worsening and mean time between admission and discharge was 15.4 days (SD 7, range 9-30). (Table 1) Bypass patency was confirmed at early (within 72h) postoperative CTA or MRA examination in all patients.

Radiological and clinical outcome

In 7 patients, the ICA and in 1 patient the MCA (M1 segment) were occluded. In all patients, a perfusion/diffusion mismatch (Type I)[18] was present on MRI before surgery (Figure 2 and 3). Perfusion/diffusion mismatch improved in all patients from a mean

mismatch of 834% to a postoperative mean mismatch of 15% with a mean imaging time before and after surgery of 2.2 months (SD 1.9). MTT, TTP and CBF ratios improved after bypass in all available patients (n=4) (Figure 2 and 3). MR diffusion ratios before and after bypass were stable in 2 patients (slight increase of 1.5-2.9%) or improved completely in 5 patients. In 1 patient MR diffusion ratio showed a progression of 55%, however without clinical correlation (case presentation below).

No patient presented neurological worsening, new morbidity and there was no mortality. Median preoperative NIHSS at admission was 4 (SD 1.7, range 2-6) for all patients and worsened to a median NIHSS of 9 (SD 3.6, range 3-15) before bypass surgery. At discharge median NIHSS was 5 (SD 3.5, range 2-12) and median mRS was 3 (SD 0.9, range 2-5). The median NIHSS improvement was of 4 points after bypass. At 3 months follow-up median NIHSS further improved to 2 (SD 2.4, range 1-8) and median mRS to 3 (SD 1, range 1-4). At last follow-up (mean 14.4 months) median NIHSS was 2 (SD 2, range 1-7) and the median mRS improved to 2 (SD 0.8, range 1-3). (Figure 4)

Case presentation

This 44-year-old woman was admitted to the Stroke Unit with dizziness and unspecific neck pain radiating behind her left ear. She had been on a diving vacation in the days before admission and suffered from an acute worsening with a transient ischemic attack (TIA) and aphasia for a couple of minutes on the day of admission. Initially she presented with an NIHSS of 2 (impaired speech, numbness) and MRI/MRA showed a dissection of the left cervical ICA and an occlusion of the inferior M2 branch with signs of acute ischemia in the left MCA territory (Figure 5A). Intravenous thrombolysis therapy with

49mg actilyse (49mg) was performed 225 minutes (3.7 hours) after TIA, but symptoms worsened the next morning to a NIHSS of 8 (disorientation, facial paresis, paresis right arm, impaired speech, numbness). DSA showed an extracranial occlusion of the left ICA and the left MCA and ACA were partially supplied by collaterals from the anterior and posterior communicating arteries (Figure 5C). Left ICA and inferior M2 occlusion could not be opened by endovascular techniques.

Aspirin 100mg/d was started and emergency bypass to augment the MCA territory was performed using an end-to-side PAA-MCA bypass. The PAA was chosen as a donor vessel, since the parietal branch of the left STA was missing in this patient and revascularization was needed in the posterior part of the left MCA territory (Figure 1). With intraoperative high-frequency ultrasound, the PAA could be localized before skin opening. The cortical recipient M4 vessel was selected using ICG videoangiography showing cortical retrograde flow (Figure 5B). Doppler flowmetry in the recipient vessel showed an increase in flow after bypass of 20ml/min (before bypass 15ml/min, after bypass 35ml/min). Preoperative perfusion/diffusion MR showed a mismatch of 750% with a diffusion restriction area of 4.68cm^2 and a TTP area of 18.92cm^2. Postoperative MRI/MRA showed excellent patency of the bypass (Figure 5A) and no intracranial hemorrhage or edema. However, MR diffusion ratio showed a diffusion progression of 55% after surgery without clinical correlate. Clinically the right arm paresis improved after the bypass surgery and NIHSS was 2 (impaired speech, numbness). The patient was discharged to neurorehabilitation on day 9 in a stable condition with a NIHSS of 2 and a mRS of 3 for neurorehabilitation. At last follow-up (24 months) the patient had resumed

her professional activity with only minimal residual deficit (NIHSS of 1 and a mRS of 1) with a patent EC-IC bypass and no new DWI lesions (Figure 5D).

Discussion

In this study we present our experience of urgent EC-IC bypass in patients presenting acute stroke. Indication for revascularization was strictly based on the following selection criteria: 1) patients with acute stroke and minor (NIHSS 1-4) to moderate stroke severity (NIHSS 5-15) at admission; 2) endovascular revascularization was not feasible or had failed as treatment option; 3) clinical worsening or symptom fluctuation (NIHSS <15) <72h after symptom onset despite best medical treatment; 4) MR perfusion/diffusion mismatch or CT perfusion/volume mismatch despite best medical treatment; 5) no large stroke (<10 cm2), edema or hemorrhage on the last imaging; and 6) patient was independent before admission (mRS<2) (Figure 6). In our study the combination of both clinical symptom worsening/fluctuation and perfusion/diffusion mismatch despite best medical treatment were the decisive criteria used as clinical surrogate marker for penumbra – indicating salvageable brain tissue. Before performing the bypass the 4 other criteria listed needed to be fulfilled to make sure that patients would get optimal first line treatment (endovascular) and to further select patients to avoid treatment futility with the bypass (stroke volume, NIHSS, pre-stroke condition).

Clear recommendations for an acute bypass in patients with acute stroke are missing. In the literature one clinical study including a control group and 5 case series or reports present data on EC-IC bypass revascularization for acute stroke with favorable patient outcome.[21-26] These studies point out that this specific patient group, which does not

achieve endovascular revascularization, and continues to present brain tissue at risk, constitutes a highly selected group and represents a small number of patients even in large reference centers. Therefore, it is crucial to collect and present all treated patient series to gain enough insight into selection criteria, therapeutic efficiency and patient outcome.

The first and most important step is to define possible selection criteria for patients that might benefit from emergent revascularization in the setting of acute stroke. Uniform inclusion criteria in the literature are rare. Two studies other than our study considered mild to moderate stroke severity as an ideal parameter to choose patients as bypass candidates.[21,22] This is based on the idea that this patient group has only a small irreversible stroke area with a sufficient collateral blood supply to keep the tissue at risk (penumbra) alive. Patients with a severe stroke or severe neurological deficits have more likely a non-reversible stroke and are therefore not considered to be candidates for surgery. Symptom worsening and fluctuation is a second key criteria to support this hypothesis by showing that the collateral blood supply is not everlasting and a bypass procedure is needed to take over blood supply in this area of risk. Besides our present study this was also a mandatory inclusion criteria for Nussbaum et al., while in the other 3 studies only a small part of patients (22-42%) developed symptom worsening or fluctuation before surgery.[21-24] The question remains if the patients without symptom progression truly needed a bypass procedure.

Radiological inclusion criteria are important parameters besides the clinical status. In 2 other studies the DWI/PWI mismatch defined as mismatch >120% and the stroke size (<20-30ml) and in one study the ratio between the volumes of Tmax >6s lesion and the

DWI lesion >1.2 were used as inclusion criteria.[21,24,26] We also used these criteria in addition to the clinical symptom worsening and believe that the combination of both is key. DWI/PWI mismatch is considered a risk factor for infarct growth without effective therapy and reperfusion therapy is recommended for these patients in the literature.[18] Lee et al. also used hemodynamic studies (diamox SPECT) to assess cerebrovascular reserve capacity (CVR) before the bypass procedure, which is an indirect sign that these patients were not in acute distress.[21] Our presented patients were not able to undergo such a procedure due to their clinical fluctuation. Since there is no evidence in the literature for the benefit of therapeutic bypass in acute stroke, we considered a functional assessment of CVR too risky in these unstable patients

In terms of outcome all studies reported good clinical and radiological outcome: E.g. Nussbaum et al. also showed that in their 13 cases of acute ischemic stroke, an acute STA-MCA bypass improved clinical symptoms and none of the patients suffered a major complication or perioperative stroke.[22] This study was not focused on radiological values to support indication for acute bypass. In comparison, Horiuchi et al. performed STA-MCA bypass surgery in 58 cases and showed that 74.1% had a favorable outcome. However, 40% of the patients showed new signs of ischemia on postoperative imaging.[23] Park et al. reported favorable outcome after bypass surgery in 76.2% of patients compared to a non surgical control group with a favorable outcome of 10.5%.[26]

In our study all eight patients achieved neurological improvement and a good clinical outcome (median NIHSS improved from 9 before bypass to 2 at LFU). Bypass was patent in all and the hemodynamic perfusion features improved. Only one patient showed asymptomatic progression of the diffusion restriction changes, the other 7 patients

showed a stable diffusion restriction ratio between before and after bypass, indicating stable stroke size. To further analyze, if the acute bypass surgery in this setting improves outcome compared to patients with conservative treatment cannot be drawn from this or any of the previously published studies.[21-24] For now we can state that all patients improved clinically and on imaging after acute bypass surgery and no major perioperative complications occurred. Besides the indication to bypass and surgical technique it is important to follow a strict anesthesia protocol to avoid any events inducing cerebral hypoperfusion such as hypotension, hypovolemia or hypocapnia.

Limitations

This series describes a single center 3 years experience of highly selected patients with acute stroke urgent bypass revascularization strategy. Definite conclusions about general safety and risk of (perioperative) complications cannot be drawn from the limited number of cases described, although all bypasses were confirmed patent and no complications occurred due to bypass surgery in this series. In all patients with early post-operative MR, perfusion and perfusion/diffusion mismatch improved and all patients improved clinically and made a good clinical recovery in this series. Despite the small number of patients the strict selection criteria clinically and on imaging allow us to report a consistent series.

Conclusions

Individualized revascularization strategies can be safely performed in an urgent setting based on a strict algorithm using clinical and imaging selection criteria in patients with

acute stroke and salvageable brain tissue. In this small series outcome was good, no mortality or new postoperative morbidity occurred.

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Figure Legend

Figure 1: End-to-side EC-IC bypass without interposition of a jump graft from posterior auricular artery to middle cerebral artery (PAA-MCA) in a patient with a dissection of the right ICA (drawn by Peter Roth)

Figure 2: Box plots showing PWI ratios of MTT, CBF, CBV and TTP as well as DWI/TTP mismatch before and early after bypass. MTT, CBF, CBV and TTP ratios

indicate normalized values of the ipsilateral stroke hemisphere in relation to the contralateral hemisphere (see also Figure 3). DWI/TTP mismatch is within the ipsilateral hemisphere only. The remarkable DWI/TTP mismatch prior to the bypass surgery returned to normal after bypass surgery as well as all other ratios improved after surgery.

Figure 3: 81 year-old-male patient (no 5) with a DWI/TTP mismatch (**A**) and a pathological MTT and TTP ratio, which completely recovered 1 week after bypass surgery (**B**)

Figure 4: Graph showing NIHSS and mRS course of all patients (n=8). NIHSS and mRS improved in all patients after bypass surgery. Note the increase of NIHSS between admission and before bypass surgery.

Figure 5: 44 year-old-female patient with (**A**) signs of acute ischemia in the left MCA territory diagnosed with a DWI/PWI mismatch including an impairment of MTT and TTP on preoperative MRI. Postoperatively there was a nearly complete recovery of the perfusion deficit with a progression of diffusion restriction of 55% after surgery without clinical correlate. (B) Based on ICG videoangiography the correct recipient vessel could be localized showing reversed and delayed flow (left) and after anastomosis ICG videoangiography showed the correct bypass flow. (**C**) DSA showed an extracranial occlusion of the left ICA to the supraclinoid segment in the PA plane (left) and partial supply by collaterals from the posterior communicating arteries in the lateral plane (middle) and anterior communicating arteries from the right ICA in the PA plane (right).

(**D**) MRI/MRA at LFU showed the patency of the bypass (left) and no new DWI lesions (right).

Figure 6: Diagram to illustrate the management of acute stroke patients to rule out patients in need of an urgent revascularization procedure.